

## Quality and Cost Assessment of 12 Brands of Amoxicillin Trihydrate 500 Milligram Capsules in Yenagoa Bayelsa State, Nigeria.

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### ABSTRACT

**Background:** Generic substitution of antibiotic capsule brands may present bioequivalence problem challenges due the preponderance of fake and substandard products in the pharmaceutical market in Nigeria, which can lead to an increase in the cost of treatment and antibiotic resistance. The study was undertaken to identify which brands of amoxicillin 500mg capsules conform to compendia standards and to compare the cost of the 12 selected brands in Yenagoa, Bayelsa State of Nigeria.

**Methods:** The study was done using the USP paddle dissolution method. The concentration, of amoxicillin in the 12 brands was determined using uv/vis spectrophotometry at  $\lambda_{max}$  272nm. Cost assessment of the brands was also carried out.

**Results:** All brands met the official specifications and in-vitro profile analysis. There was a good percentage price margin for the sales of all brands except Amox4.

**Conclusion:** The in-vitro dissolution profile tests were satisfactory. A uniform pricing system for the tested brands was lacking. The retail prices were unaffordable.

**Key words:** brands, amoxicillin, dissolution, cost, spectrophotometry.

### INTRODUCTION

Amoxicillin trihydrate 500mg capsule is one of the various dosage forms of amoxicillin employed in the treatment of susceptible bacterial infections in our society. It is prescribed at all levels of health care delivery. It is available as prescription only medicine and it is one of the most prescribed antibacterial agents<sup>1</sup>. The Nigeria essential drugs programme fosters generic prescribing and generic substitution during the dispensing process. Consequently interchangeability with amoxicillin capsule generic brands may lead to therapeutic failure, increased cost of treatment, and development of resistance to the drug when Bioequivalence problems arise if a brand is fake, false or/and substandard<sup>2</sup>.

Generics are 'copies' of innovator and patented drugs and can be marketed at lower cost following expiration of patent right of the innovator brand. The main purpose of generic drug manufacturing is to encourage mass production of marketed drugs and reduce the price of drugs in line with the provisions of the essential drug list(EDL); ultimately to lower public health costs and make health care delivery more affordable. Bioequivalence or bioavailability studies are required for the registration of generic branded drug

formulations. A study carried out by Kyriacos *et. al.* (2008) on the quality of amoxicillin formulations in some Arab countries revealed that fifty-six percent of amoxicillin capsules did not meet the United State Pharmacopeia (USP) requirements. Majority had amounts bordering the lower limit. Individual average values as low as 59% of the label claim were detected. 8% of the samples of suspensions gave measurements below pharmacopeial limits. This research suggested a high existence of substandard drugs in some Arab market where several factors might jeopardize the quality status of medicines, such as; lack of effective quality assurance system during manufacture in both Arab and export countries, and uncontrolled storage conditions, especially unsuitable pharmacy premises. Use of substandard antibiotic preparations increases the risk of therapeutic failure and the emergence of drug-resistant microorganisms. A study carried out by Ejele *et. al.* (2011) on the Determination of Amoxicillin concentration in proprietary capsules obtained in Nigeria showed that the concentration of all amoxicillin brands studied were close to each other and within the allowed pharmacopoeia specification for amoxicillin 500mg capsule, which lies between 480-520 mg/cap. A study by

Karlage and Myrdal of the College of Pharmacy, University of Arizona in 2005 compared the content uniformity and weight variation for amoxicillin capsules 500 mg, amoxicillin/clavulanic acid suspension 457mg/5mL, and furosemide tablets 40 mg using high performance liquid chromatography (HPLC). The content uniformity for the amoxicillin capsules was found to be  $15.4 \pm 2.4\%$  and  $99.4 \pm 9.3\%$ , for Mexican and United States of America (USA) capsules, respectively. The percent relative standard deviation (% RSD) for weight variation was found to be 8.7% and 1.5% for capsules obtained from Mexico and the United States of America (USA) respectively. Content uniformity analysis for the Mexican suspension product resulted in an average of  $85.5 \pm 1.2\%$  for amoxicillin and  $98.6 \pm 1.9\%$  for the clavulanic acid content, while the results for the U.S. suspension product were  $104.4 \pm 3.1\%$  and  $117.8 \pm 3.6\%$  for amoxicillin and clavulanic acid, respectively. Content uniformity for the furosemide tablets was found to be  $90.3 \pm 4.8\%$  and  $95.6 \pm 2.1\%$  for Mexican and U.S. tablets, respectively. The % RSD of weight variation for the Mexican tablets was 2.1%, while the % RSD for the U.S. tablets was found to be 1.0%. From the three products tested, content analysis revealed that the amount of active ingredients for two of the products acquired in Mexico were appreciably lower than the concentrations for product from the U.S.A.

Amoxicillin is one of the most commonly prescribed drugs for infectious diseases. It is a well known fact that with the advent of generic and multi sources of drug products,

issues surrounding free interchangeability and substitution of brands have arisen<sup>1, 2</sup>. Coupled with this, is the flooding of the pharmaceutical market with fake and substandard products; it has become necessary to evaluate some brands of amoxicillin that are sold or available in Bayelsa state. Bacterial infections have long posed a major threat to human existence. Antibiotics which are also known as magic bullets have been used to combat this problem. Amoxicillin 500mg capsule is one of the major antibiotics that are mostly used in the treatment of infections, amoxicillin is available in Nigeria as single unit dosage forms; they are made in hard gelatin capsule forms, thus masking any unpleasant taste; they are for oral administration. These factors therefore make it easy to administer orally by patients. With the advent of multiple source of drugs, there is need to test the various brands available in the market to ensure that they conform to compendial standards and ensure patient safety. This study was undertaken to determine which of the test brands meet compendial standard rate of dissolution and to compare the various costs of 12 selected brands of amoxicillin 500mg capsules available in Yenagoa.

## MATERIALS AND METHODS

### Materials

Twelve (12) brands of marketed amoxicillin trihydrate 500mg capsules and Amoxyl (Beecham) 500mg were purchased from various pharmacies in Yenagoa, Bayelsa state; Veegoo dissolution paddle apparatus-made available for use in the pharmaceuticals and technology laboratory of the Niger Delta University, Wilberforce island, Bayelsa State. A uv-vis

spectrophotometer was used for analysis. A chemical balance for weighing individual capsules and distilled water.

### Methods

Twelve (12) brands of marketed amoxicillin trihydrate capsules were purchased from various pharmacies in Yenagoa, Bayelsa state. The samples were checked for their NAFDAC registration number, manufacturing date, expiry date, and batch number before purchasing. The selling price and wholesale prices as well as the address of manufacturer of each brand were noted and recorded. The samples were coded as Amox 1, Amox 2, Amox 3, Amox 4, Amox 5, Amox 6, Amox 7, Amox 8, Amox 9, Amox 10, Amox 11, and Amox 12.

### Weight Uniformity test

10 capsules randomly chosen from a brand were accurately weighed individually; care was taken to preserve the identity of each capsule. The contents of each capsule were removed and the empty capsule shells were weighed individually. The net weight for each capsule was obtained by subtracting the weight of the shell from the respective gross weight. This was repeated for all brands. The mean weight for each brand was calculated. Source of variation for content uniformity among the twelve brands was determined using a one way analysis of variation to determine the *F* and *P*-values respectively

### In vitro dissolution test

The tests were conducted at  $37 \pm 0.5^\circ\text{C}$  using a USP specification dissolution rate test type II apparatus (Paddle apparatus) made available in the pharmaceuticals and technology laboratory (veegoo dissolution apparatus) according to

the United States Pharmacopeia and The National Formulary (USP 30 -25, 2007). For *in vitro* dissolution studies, water was used as dissolution medium. The water-bath temperature was fixed and confirmed to be  $37\pm 0.5^{\circ}\text{C}$  before starting the experiment. The medium (water) was preheated and maintained at  $37^{\circ}\text{C}$  and then a quantity of 900 ml was added to each vessel. The apparatus was then assembled and paddle rotation was started and adjusted to 75rpm and the system was allowed to equilibrate for 15 minutes. After that, the paddle rotation was stopped and three capsules from same code were placed in the vessels (one capsule per vessel) and allowed to sink to the bottom. The apparatus was immediately operated at 75 rpm. Each vessel, vessel position, and corresponding sample result were assigned the same code. The duration of the experiment was 60 minutes for each set of sample. 10mL of the sample solution was withdrawn at the end of 2, 5, 10, 15, 30, 45 and 60 minutes from each dissolution vessel, and replaced with 10mL of distilled medium after each sample withdrawal to maintain sink conditions.

#### Spectrophotometry assay

The dissolution solution was filtered, and subjected to uv-vis spectrophotometer to obtain the absorbance at 272nm for amoxicillin trihydrate by UV Spectrophotometer single beam. The amount of drug present in the samples was calculated from standard calibration curve using standard Amoxyl cap made by Beecham (GSK) at concentrations of 0.0125mg/ml, 0.025mg/ml, 0.05mg/ml, 0.1mg/ml, 0.15mg/ml, 0.2mg/ml, 0.25mg/ml, 0.3mg/ml, 0.45mg/ml, 0.5mg/ml. The percentage of drug dissolved was also calculated with respect to time. For each sample, three measurements were taken and the mean

concentrations were determined. The calibration curve for the absorbance versus the standard concentration of Beecham Amoxyl was done using Microsoft Excel 2007 package.

#### RESULTS

Sample test products were obtained from nine community pharmacies, two government hospitals and one private hospital. All the sample products, Amox 1-12 had batch number, date of manufacture, expiration date, NAFDAC number, and name of manufacturer as well as the address of local (Nigerian) manufacturer/marketer. Two Private Community Pharmacies 7 and 8 claimed to have obtained their stock of Amoxy 7 and 8 from the Lagos market, while the private hospital did not reveal its source(see table 1). Others however, claimed to have obtained their stock directly from the pharmaceutical sales representatives of pharmaceutical companies. Seven private community pharmacies sold 100capsules of Amoxicillin 500mg at N1000, while the 2 government health facilities sold at N1000 and N1500. Two private community pharmacies sold its own at N4000; the private hospital sold its own at N2000. The cost price of sample products of 100 amoxicillin trihydrate capsules 0.5g ranged from N350 to N3000 with three pharmacies having a cost price of N350, two pharmacies having a cost price of N500, and another two pharmacies with a cost price of N550. (Table 1). The selling price of sample products of 100 amoxicillin trihydrate capsules 0.5g ranged from N1000 to N4000. Majority of facilities had a selling price of N1000 for 100 amoxicillin trihydrate capsules 0.5g. The percentage price margin of sample products ranged from 33.3% for Amox 11 to 328.6% for Amox 2. However, a percentage price margin of 1042.9% was recorded for Amox 6. Six sample products had a percentage price margin of 100% and above,

while five sample products had a percentage price margin below 100% ( table 1). The content uniformity of sample products ranged from  $0.50\text{g}\pm 0.01$  for Amox 2 to  $0.60\text{g}\pm 0.02$  in Amox 3. Four samples had its mean content  $0.59\text{g}\pm 0.01$  (Amox 5, 8, 11, and 12). The individual content of sample products was observed to range from 0.47g (for Amox 7) to 0.62g (for Amox 3). The overall mean content of all the sample products was  $0.56\pm 0.04\text{g}$ . The result of the analysis of variation(ANOVA) for content uniformity of the 12 selected brands of amoxicillin 500mg capsules showed a significant difference in contents uniformity . The  $F$ -value = 3.8950 and the  $P$ -value=0.0002352<0.001( see table 2). The concentration of amoxicillin trihydrate capsules that dissolved in water ( $37^{\circ}\text{C}$ ) in the dissolution test at the end of 60mins for the sample products ranged from 0.41mg/ml (Amox 1) to 0.74mg/ml (Amox 9) with a percentage release ranging from 82.81% to 147.13%. At the time of 15mins, the amount of amoxicillin trihydrate released into the dissolution medium ranged from 0.26g (52.15%) for Amox 3 to 0.67g (134.16%) for Amox 9. At time 30mins the amount of drug concentration recovered ranged from 0.32g (63.91%) to 0.72g (144.31%). At time 45mins, the amount of amoxicillin trihydrate released ranges from 0.38g (76.58%) for Amox 1 to 0.73g (146.04%) for Amox 9( table 3). At time 60mins, the amount of amoxicillin trihydrate released ranged from 0.41g (82.81%) for Amox 1 to 0.74g (147.13%). Also, at 60mins, six sample products (Amox 2, 5, 6, 8, 11, 12) had a percentage release above 120%, while six sample products (Amox 1,3, 4, 7, 8, 10) had a percentage release below 120%, but were all above 80%. The linear regression coefficient  $r$  for the standard calibration curve was 0.947892(Figure 1).

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Table 1. Summary of costs of sample brands of amoxicillin 500mg capsules

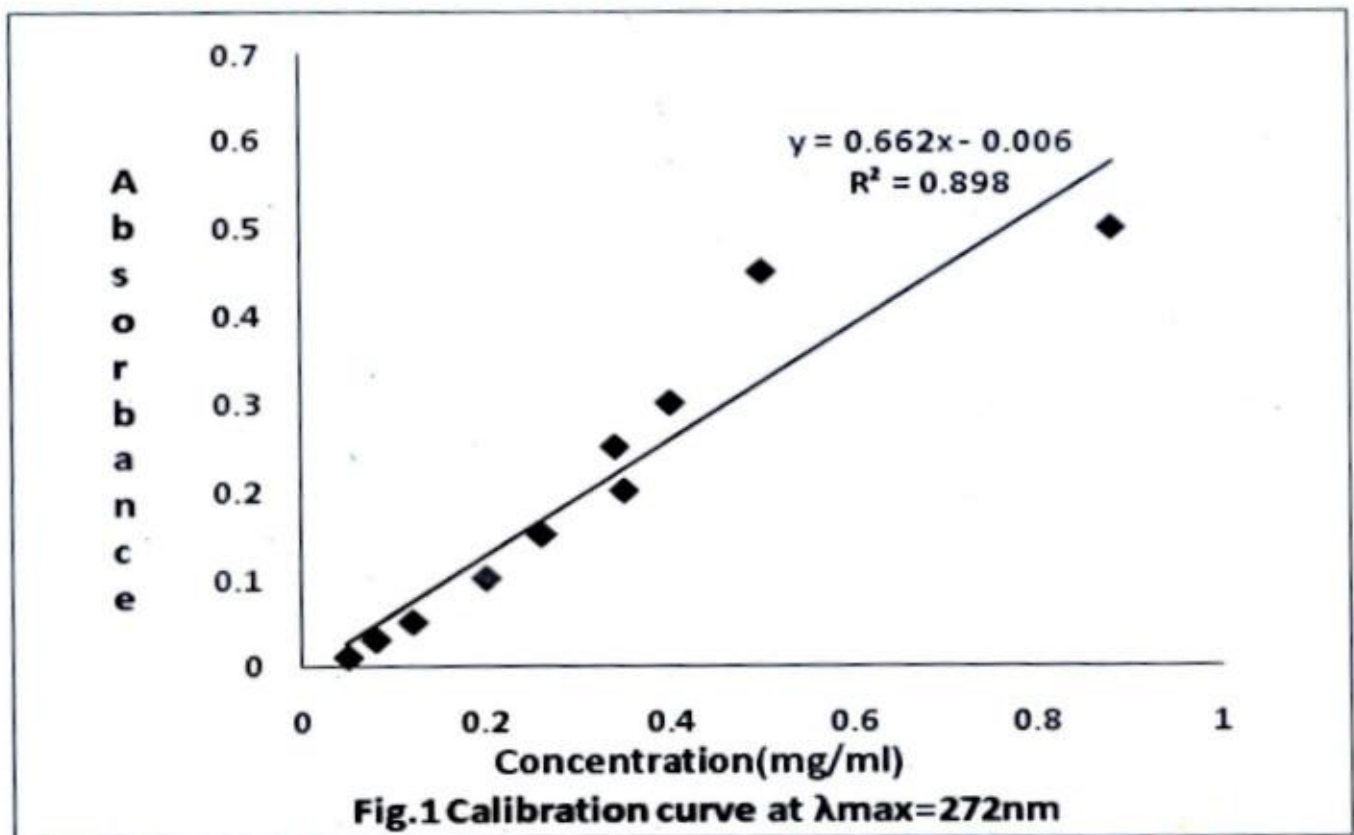
Brand	Cost price in Naira of 100 capsules	Selling price in Naira of 100 capsules	Price margin in Naira	Price margin in %	Source of Purchase
Amox 1	Undetermined	2000	Undetermined	Undetermined	Undetermined
Amox 2	350	1500	1150	328.6	Community Pharmacy
Amox 3	350	1000	650	185.7	Company Sales Rep
Amox 4	700	1000	300	42.9	Company Sales rep
Amox 5	480	1000	520	108.3	Company Sales Rep
Amox 6	350	4000	3650	1042.9	Company Sales Rep
Amox 7	500	1000	500	100	Company sales rep
Amox 8	600	1000	400	66.7	Company sales rep
Amox 9	500	1000	500	100	Company sales rep
Amox 10	550	1000	450	81.8	Lagos market
Amox 11	3000	4000	1000	33.3	Lagos market
Amox 12	550	1000	450	81.8	Company sales rep

Table 2. Analysis of variance for test of content uniformity for the 12 selected amoxicillin capsule brands

Source of variation	SS	d.f	MS=SS/d.f	F-value	P-value
Between groups	0.1623	9	0.1803	3.8950	0.0002352
Within groups	0.5138	111	0.004629		
Total	0.6700	120			

**Table 3. Capsule content and dissolution parameters**

Brand	Mean content (gms)	Concentration in grams/ml released at 60mins (gm/ml)	Percentage concentration released at 60mins
Amox 1	0.51±0.01	0.41	82.81
Amox 2	0.50±0.01	0.63	126.02
Amox 3	0.60±0.02	0.6	119.65
Amox 4	0.59±0.02	0.55	109.05
Amox 5	0.59±0.01	0.67	133.56
Amox 6	0.58±0.01	0.71	141.40
Amox 7	0.50±0.05	0.42	84.84
Amox 8	0.59±0.01	0.57	114.67
Amox 9	0.57±0.01	0.74	147.13
Amox 10	0.50±0.04	0.57	114.22
Amox 11	0.59±0.01	0.65	130.77
Amox 12	0.59±0.01	0.68	136.31



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## DISCUSSION

All sample products were in conformity with the legal (NAFDAC) requirements for product labelling. The expiration date is the actual date placed on the drug pack indicating the expected shelf life of the product if stored under specified optimal conditions after which its potency cannot be guaranteed. The cost prices and the sources of purchase for the sample products were revealed by all the pharmacy premises visited except in the premise where Amoxy 1 was purchased. This may be indicative of a doubtful source of drug procurement which is contrary to the provisions of the Pharmacy laws. Nine pharmacy premises revealed that they procured the various drugs from the respective company's sales representatives. This is in accordance with the provisions of the pharmacy code of ethics and the Poison and Pharmacy Act which provides that pharmacies shall obtain their drug products from authorized sources only. However, two pharmacy premises revealed that the drugs were purchased from the Lagos market, which is contrary to the Poison and Pharmacy Act.

The mean content of samples ranged from 0.50g to 0.60g. While the labelled weight of sample products was 0.5g. The statistical significant variations of weight content among samples could be attributed to the various methods and techniques individual pharmaceutical company production procedures as well as the different excipients used in the preparation of the sample products. The United States pharmacopoeia U.S.P (2005) provides that not more than one of the individual weights of the ten tablets should deviate outside the range of 75% to 125% of the average. All samples were within the given limit for uniformity of weight for capsules and thus, they can be said to have passed the uniformity of weight test. The above finding is in consonance with a report In 2011 on the determination of Amoxicillin concentration in proprietary capsules obtained in Nigeria<sup>3</sup>. The results

obtained showed that the concentration of all amoxicillin brands studied were close to each other and within the allowed pharmacopoeia specification which compares favourably to that reported by in 2005, on the content uniformity and weight variation for three medicinal products obtained from pharmacies in Mexico and the United states<sup>4</sup>.

The *in-vitro* dissolution profile of a drug can be as an indicator of the *in-vivo* bioavailability of a drug product. The sample products were found to have dissolved to various degrees at different time intervals. At 60minutes which is the time limit prescribed by the USP, all the sample products had more than 80% dissolution. The USP 2005 provides that not less than 80% of the labelled amount of amoxicillin trihydrate should be dissolved in 60 minutes. All the tested drug samples were above 80% dissolved at 60minutes. Therefore all the brands of amoxicillin tested were satisfactory. The above finding is in consonance with the report by In 2009, on the pharmacokinetic study of amoxicillin capsules in Healthy subjects in Bangladeshi<sup>5</sup>. However, 6 brands (Amox 1, 3, 4, 7, 8, and 10) each had a percentage release of less than 120% at 60mins. According to the report by Kiron *et. al.* in 2011 on the influence of storage conditions on the potency of amoxicillin, the study revealed that there is an accelerated degradation of amoxicillin in regions of higher humidity<sup>6</sup>. Also, the report by Naidoo *et. al.* in 2006 showed that only those amoxicillin capsules stored between 20 to 25°C, and protected from moisture were stable for 14days<sup>7</sup>.

Five brands (Amox 2, 5, 6, 9, 11, and 12) had a relatively higher percentage release above 120%. This is however unrealistic. For instance, Amox 9 had a percentage release of 147.13%. This translates to 0.74g of the drug being

released which is about one and a half times of the stated weight of the drug. This could translate to an over dosing of the drug when used in therapy. This should not be encouraged. Also, it is known that molecules in solution can aggregate. The cost price of the sample products ranged from ₦350 to ₦3000 with Amoxy 8 having the highest cost price of ₦3000 per pack of 100 caps of amoxicillin trihydrate 500mg capsules. The various selling prices were observed to which ranged from ₦1000 to ₦4000 per pack of 100 caps of amoxicillin trihydrate 500mg capsules. Amoxy 6 and Amoxy 11 having the highest selling price of ₦4000 per pack of 100 caps of amoxicillin trihydrate 500mg capsules. This confirms that there is no price uniformity. In addition, people pay a lot more for same products as was observed by WHO/FMOH (2006) that the costs of medicines in Nigeria were two (2) to sixty-four (64) times the international cost of the same medicine. It was observed that 5 sample brands Amox 4, 8, 10, 11, and 12 were to be sold at a price of less than 100% price margin in their respective premises. There was no uniform pricing system for amoxicillin trihydrate capsules sold in Bayelsa State. However, the sale of the various brands of amoxicillin trihydrate capsules sold generated a good profit margin for. 50% of the tested brands (Amox 2, 3, 5, 6, 7, and 9) were all observed to have a percentage margin ranging from 100% to 1042.9%. This is a very high profit margin. Amox 7 and Amox 9 both have a percentage price margin of 100%. Amox 6 was observed to have the highest percentage margin rate of 1042.9%. The WHO (2006) report had indicated that medicines were largely unaffordable because of high cost and profiteering. The cost analysis of these drugs showed that they may not be favourable for patients especially the low income earners. Amox 11 and 12 which had a low percentage margin were both obtained from private pharmacy premises. This could be as a result of a possible market strategy. However, the premises were found to be wholesale outlets whose business and operation depended more on

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turnover and volume of sales. Amox 2, 5, 6, 9, 11, and 12 had a relatively high percentage release of above 120%. Amox 3, 4, 7, 8, and 10 each had a percentage release of less than 120% at 60mins. The cost analysis of these samples gave a relatively low percentage price margin. These products are therefore more affordable by patients. These sample products also conformed to compendial standards. Amox 11 was observed to have a percentage price margin of 33.3%. This was the lowest percentage price margin observed amongst the drug samples obtained from the different premises. However, the source of purchase of Amox 11 was not in accordance with the provision by the pharmacy code of ethics and the Poison and Pharmacy Act stated above, as it may have been purchased from unauthorized source. Therefore, Amox 8 from a government owned premise as the cheapest for patients. The source of purchase is in line with the provision of the pharmacy code of ethics and the Poison and Pharmacy Act. Various factors however could influence the price of drugs in a facility and some of which are; accommodation rent, transportation of drugs, payment of employed staffs and bills, e.t.c.

## CONCLUSION

The tested samples (Amox 1 capsules to Amox 12 capsules), containing amoxicillin trihydrate 500mg are registered by NAFDAC and are available in Bayelsa state. Most premises sold 100capsules of amoxicillin trihydrate 500mg at ₦1000. However, there was no uniform pricing system for the various brands of amoxicillin trihydrate 500mg capsules available in Bayelsa state.

The dissolution profiles of the tested samples were within the prescribed limit at 60minutes, meaning that the capsules are likely to dissolve and be readily absorbed when administered orally. Therapeutic failure is not likely to occur from the use of any of the tested brands. The quality of tested

products was satisfactory. It is important therefore for pharmacist to regularly check the quality of their stock of amoxicillin and other products and for pharmacy premises to have basic quality control policies in order to ensure safety of products for the consuming populace.

There is however, need for the pricing system of these products to be regulated in order to prevent profiteering. Some of the results from the cost analysis showed that some of the prices of these products were outrageously high. This could constitute a drug therapy problem in the community with limited choice for substitution of brands.

The source of purchase of these products should also be closely monitored to ensure that all drugs available for patients use are from a reliable source.

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